DETAILED ACTION

Status of Claims

1. Claims 1-19 are pending in this application.

2. Addition of new claims 17-19 is acknowledged.

3. Claims 1 and 8-11 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6/16/10.

4. Claims 2-7 and 12-19 are examined.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The rejection of claims 2-7 and 12-16 under 35 U.S.C. 103(a) as being unpatentable of Simon et al in view of Trotter et al and/or Heckenmuller et al has been modified as follows, as necessitated by Applicant's amendment filed 6/2/11:

7. Claims 2-7 and 12-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simon et al (EP 391396, cited by Applicants) in view of Trotter et al (J. Clin. End. Metab., 84(12), 4531-4535, 1999, cited by Applicants) and/or

Heckenmuller et al (US Patent 5,514,673), and in view of Chen et al. (US Patent 6,267,985) and/or Applicant's admission in the specification.

The claimed invention, as amended, is drawn to a hormone-containing isotonic oil emulsion for intravenous administration comprising at least one progestagens and at least one estrogen; an oil phase; an antioxidant; an emulsifier; and an aqueous phase; wherein the at least one progestagens and the at least one estrogen are dissolved in the oil phase prior to being mixed with the aqueous phase, and the oil phase comprises oils of marine origin (see claim 2) such as fish oils (new claim 17).

Simon et al teach medicinal oil-in-water emulsions comprising an effective amount of a lipophilic drug, MCT oil optionally in combination with vegetable oil, about 0.05-20% of phospholipid (emulsifier), about 0.03-10% of a non-ionic surfactant (co-emulsifier) and about 0.05-5% of an ionic surfactant (co-emulsifier) (abstract). The compositions may further comprise an antioxidant such as α-tocopherol (page 5, lines 1-2); compositions comprising α-tocopherol are exemplified (Examples 1 and 2). The compositions are suitable for parenteral administration (page 4, lines 9-10), including intravenous administration (page 5, lines 19-22). Suitable hydrophobic drugs include lipophilic steroids, such as progesterone (page 5, lines 3-8). The compositions may be prepared by preparing an oily solution comprising oily carrier and hydrophobic drug, and then mixing the oily solution with the aqueous solution (see page 5, lines 23-34).

While Simon et al teach that progesterone may be one of the lipophilic drugs employed in the emulsion, Simon et al do not specifically teach an emulsion which

includes progesterone and estrogen. Simon et al also do not specifically teach that the oil carrier may also comprise oils of marine origin.

Trotter et al teach an oil-in-water emulsion of an estradiol (an estrogen) and pregn-4-ene-3,20-dione (progesterone, a progestagen) in a phospholipid-stabilized soybean oil emulsion, administered as an IV infusion (see page 4532, 1st column). Trotter et al teach that administration of progesterone and estradiol in extremely preterm infants provides benefits including improved bone mineral accretion and less chronic lung disease (abstract and page 4535).

Heckenmuller et al teach a pharmaceutical composition having a form suitable for transmucosal administration containing progesterone and/or estradiol as an active ingredient (abstract). In its background discussion, Heckenmuller et al teach that parenteral administration of the sex hormones is known, albeit with inconveniences (col. 1, lines 15-38). Heckenmuller et al teach that its formulation can be manufactured by conventional methods for preparing two-phase emulsion systems, whereby progesterone and/or estradiol are dissolved in the oil be used prior to admixing with the aqueous phase (col. 3, lines 5-11).

Chen et al teach oil-containing pharmaceutical compositions for solubilization of triglycerides and improved delivery of therapeutic agents (abstract). Conventionally, the therapeutic agent (soluble in oils, or triglycerides) is solubilized in a bioacceptable triglyceride solvent, such as a digestible vegetable oil, with the oil phase dispersed in an aqueous solution. Such triglyceride-containing formulations suitable for delivering therapeutic agents through an aqueous environment is an oil-in-water emulsion (col. 1,

lines 12-30). Preferred triglyceride solvents include vegetable oils, fish oils, and medium-chain triglycerides (col. 7, lines 14-17). Oil-soluble therapeutic agents which may be used include progesterone (column 31).

Applicant's specification states lipid emulsions containing vegetable oils and/or medium-chain triglycerides (MCT) and/or marine origin (e.g., fish oils) are "known to the skilled person from the prior art" (page 7, lines 6-10 of the specification).

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to administer progesterone and estradiol in the oil-in-water emulsion of Simon et al; thus arriving at the claimed invention. One skilled in the art would be motivated to do so because the administration of progesterone and estradiol provides the benefits of improved bone mineral accretion and less chronic lung disease, as taught by Trotter et al. One would reasonably expect success from the administration of progesterone and estradiol in the oil-in-water emulsion of Simon et al because Simon et al fairly teach and suggest that lipophilic steroids, including progesterone, may be used in its emulsion, and because Trotter et al teach that progesterone and estradiol may be administered in phospholipid-stabilized oil-in-water emulsions.

Additionally or alternatively, it would have been obvious to a person having ordinary skill in the art at the time the invention was made to administer progesterone and estradiol in the oil-in-water emulsion of Simon et al by dissolving the hormones in the oil phase prior to being mixed with the aqueous phase; thus arriving at the claimed invention. One skilled in the art would be motivated to do so, with a reasonable

expectation of success, because dissolving said hormones in the oil phase prior to being mixed with the aqueous phase is a conventional method for preparing two-phase emulsion systems, which would include those formed for parenteral use, as taught by Heckenmuller et al. (It is noted that, while Heckenmuller et al teach that there are "inconveniences" associated with parenteral (e.g., intravenous) use, such as the need for sterile delivery devices and medical assistance, Heckenmuller et al also teach that parenteral administration does provide the benefit of circumventing the undesired first pass effect (from oral administration), and the "inconveniences" noted by Heckenmuller do not prevent its emulsion from being used for intravenous administration.)

Regarding the addition of fish oils in the oil carrier, it would have been obvious to a person having ordinary skill in the art at the time the invention was made to include fish oils as part of the oil carrier in the composition of the combined references; thus arriving at the claimed invention. One skilled in the art would have been motivated to do so because vegetable oils and medium-chain triglycerides, and fish oils, are all preferred triglycerides in pharmaceutical oil-in-water emulsion compositions comprising oil-soluble therapeutic agents as taught by Chen et al, and therefore are functionally equivalent to one another. Therefore, it would be well within the purview of the skilled artisan to choose either compound or any combination thereof as the oil carrier of the composition of the combined references, since the prior art establishes the functional equivalency of fish oil and other triglycerides (vegetable oils and medium-chain triglycerides). Additionally or alternatively, since Applicant's specification states that lipid emulsions comprising vegetable oils and/or MCT and/or oils of marine origin (e.g.,

fish oils) are "known to the skilled person from the prior art", it would be within the purview of the skilled artisan to include marine oils (e.g., fish oils) with an oil carrier of vegetable oils and MCTs, as admitted by Applicants.

Regarding claims 3 and 4, Trotter et al teach that the concentration of estradiol is between 2.2 ng/ml and 0.22 mg/ml, and the concentration of pregn-4-ene-3,20-dione is between 0.4 ug/ml and 1.25 mg/ml (page 4532, 1st column). These concentrations result in ratios of 6.25:1 (1.25 mg/ml to 0.22 mg/ml) and 181:1 (0.4 ug/ml to 2.2 ng/ml). These ratios are within Applicant's range of from 2:1 to 200:1.

Regarding claim 4, Trotter et al teach that the concentration of estradiol is between 2.2 ng/ml and 0.22 mg/ml (which is equivalent to 0.00000022 – 0.022% by weight), and the concentration of pregn-4-ene-3,20-dione is between 0.4 ug/ml and 1.25 mg/ml (which is equivalent to 0.00004 – 0.125% by weight (page 4532, 1st column). These amounts overlap those of the claimed invention; one skilled in the art would be motivated to manipulate the amounts of estradiol and progesterone within said ranges by routine experimentation, in order to optimize the efficacy of the resultant composition.

Additionally or alternatively regarding claims 3 and 4, Heckenmuller et al exemplify amounts of estradiol of 0.055 and 0.068%, and amounts of progesterone of 0.967 and 1.2% (Examples 3-6), which result in a ratio of approximately 18:1; these values are within Applicant's ranges taught in claims 3 and 4.

Regarding claim 5, Trotter et al teach that the active agents used are progesterone and estradiol (abstract and page 4532).

Regarding claim 6, Simon et al teach use of mid chain triglycerides (abstract) such as Miglyol 812 (C8-C10 triglycerides) (page 4, lines 30-31).

Regarding claim 7, Simon et al teach amounts of phospholipid of 0.05-20% (abstract). This range overlaps that of the claimed invention; one skilled in the art would be motivated to manipulate the amount of phospholipid from within said ranges by routine experimentation, in order to optimize the stability of the resultant composition.

Regarding claims 12 and 13, Simon et al teach amounts of non-ionic surfactant of 0.03-10% and ionic surfactant of 0.05-5% (abstract). These amounts overlap those of the claimed invention; one skilled in the art would be motivated to manipulate the amount of phospholipid from within said ranges by routine experimentation, in order to optimize the stability of the resultant composition.

Regarding claim 14, Simon et al teach that the compositions may further comprise an antioxidant such as α-tocopherol (page 5, lines 1-2).

Regarding claim 15, Simon et al exemplify amounts of α-tocopherol of 0.05% of the emulsion, and 20.55% of oil phase (Example 1). Therefore, the amount of α-tocopherol would be equivalent to 0.24% of the oil phase, or 240 mg based on 100 g of the oil phase. This amount is within Applicant's range of 10mg to 1000mg based on 100g of the oil phase.

Regarding claim 16, Simon et al teach that the more preferred pH is 6.0-8.0, especially for parenteral administration (page 4, lines 28-29).

Regarding claims 18 and 19, Simon et al teach the use of MCT oil optionally in combination with vegetable oil (abstract).

Response to Arguments

8. Applicant's arguments filed 6/2/11 have been fully considered but they are not persuasive.

In response to Applicant's arguments that Trotter and Heckenmuller teach away from the claimed invention (pages 9-10 of Remarks filed 6/2/11), these arguments are not persuasive because, while Trotter does teach adding estradiol and progesterone to ethanol prior to adding to the emulsion, there is nothing in the teaching of Trotter that would lead one skilled in the art to believe that the emulsion could not also be formed by adding the estradiol and progesterone to the oil phase prior to forming the emulsion, as taught by Simon and Heckenmuller. Furthermore, it is noted that the claims are drawn to the emulsion itself, not a process of making it, and therefore the limitation "wherein the at least one progestagens and the at least one estrogen are dissolved in the oil phase prior to being mixed with the aqueous phase" amounts to a product-by-process limitation. Since the same product is obtained when the estradiol and progesterone are added to the formed emulsion as when they are added to the oil phase prior to forming the emulsion, the emulsion of the combined references meets the limitations of the claim.

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) MPEP 2113. See also In *SmithKline Beecham Corp. v. Apotex Corp.*, No. 04-1522 (Fed. Cir. February 24, 2006).

Furthermore, even if a different product is formed when the hormones are added to the oil phase prior to mixing with the aqueous phase, instead of adding the hormones to the formed emulsion, Simon teaches that the lipophilic drugs may be added to the oil phase separately prior to forming the emulsion (page 5, lines 23-27). Simon specifically teaches that lipophilic steroids are hydrophobic drugs that may be added to the oil phase, and cites progesterone as an example (page 5, lines 4-27); therefore, one skilled in the art would reasonably expect that estradiol, another lipophilic steroid, could also be added to the oil phase prior to mixing with the aqueous to form the emulsion. Additionally, adding progesterone and estradiol to the emulsion by dissolving them in the oil phase prior to being mixed with the aqueous phase is a conventional method for preparing two-phase emulsion systems, as taught by Heckenmuller et al (see rejection, above). Regarding Heckenmuller, it is noted that, while Heckenmuller et al teach that there are "inconveniences" associated with parenteral (e.g., intravenous) use, such as the need for sterile delivery devices and medical assistance, Heckenmuller et al also teach that parenteral administration does provide the benefit of circumventing the undesired first pass effect (from oral administration), and the "inconveniences" noted by Heckenmuller do not prevent its emulsion from being used for intravenous administration.

In response to Applicant's argument that a skilled artisan would be discouraged from using oils which are high in unsaturated fatty acids or longer chain lengths, such as oils of marine origin including fish oils, based on teachings from Simon and Heckenmuller (pages 11 and 12 of Remarks), this argument is not persuasive because

Simon specifically teaches that oils of longer chain lengths (vegetable oils) may be included with MCT (e.g., see page 3,line 47), and Heckenmuller teaches that artificial or natural oils, or mixtures thereof, can be used (col. 2, lines 55-56), and neither reference discourages the use of longer-chain triglycerides. Additionally, Chen teaches that preferred triglycerides in oil-water emulsions containing oil-soluble therapeutic agents include fish oils as well as vegetable oils and medium-chain triglycerides (col. 7, lines 14-17), and thus it would be within the purview of the skilled artisan to include oils of marine origin, such as fish oils, with the oil carrier of the combined references. Furthermore, Applicant's own specification states lipid emulsions containing vegetable oils and/or medium-chain triglycerides (MCT) and/or marine origin (e.g., fish oils) are "known to the skilled person from the prior art" (page 7, lines 6-10 of the specification), and therefore Applicant's assertions that the skilled artisan would be discouraged from using such oils are not well founded.

Therefore, it is the Examiner's position that the claims are rendered obvious.

Claim Objections

9. Claims 2 and 3 are objected to because of the following informalities: the claims recite the phrase "at least one progestagens and at least one estrogen" (lines 3 and 8 of claim 2 and lines 2-3 of claim 3). It appears that the term "progestagens" should read "progestagen". Appropriate correction is required.

Response to Arguments

10. Applicants have not responded to the objection to claims 2 and 3. Accordingly, the objection is maintained for reasons of record.

Conclusion

No claims are allowed at this time.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BARBARA FRAZIER whose telephone number is (571)270-3496. The examiner can normally be reached on Monday-Thursday 9am-4pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on (571)272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BSF

/Joanne Hama/
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